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09/918,873	07/31/2001	Elizabeth J. Goldsmith	A33864 090495.0232	2430

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EXAMINER
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NASHED, NASHAAT T

ART UNIT	PAPER NUMBER
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1652

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DATE MAILED: 08/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.  
**09/918,873**

Applicant(s)  
**Goldsmith et al.**

Examiner  
**Nashaat T. Nashed**

Art Unit  
**1652**



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on Jun 6, 2003
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above, claim(s) 1-31 and 34-40 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 32 and 33 is/are rejected:
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some\* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_ 6) ☐ Other:

Applicant's election with traverse of Group III, claims 32 and 33 in Paper No. 10 is acknowledged. The traversal is on the ground(s) that it is burdensome on the applicant to file 134 application which is required by the imposed restriction. Applicants appear to accept the restriction requirement between Groups A-C, but would like the restriction within each of Groups A-C to be vacated and replaced with an election of species. In order to support applicants position, they cite *In re Watkinson*, 14 USPQ. 2d 1407 (Fed. Cir. 1990). This is not found persuasive because the excessive burden of search to examine all the independent compounds and methods claimed in each of Groups A-C, 63 inventions for each of Groups A and B, and 8 inventions of Group C according to the applicants. Indeed, if applicants find it burdensome to file 134 applications, applicants must understand the search burden on the examiner and the Office to properly search all the independent inventions comprised in each of Groups A-C together. As indicated in the previous Office action, paper number 10, the restricted embodiment of Group A-C are either independent chemical compounds having different structure and function, or independent methods having different steps, objectives and results. It should be noted that the generic claims involve any protein kinase from any biological source, see elected claim 32 for example. As of the court opinion *In re Watkinson*, it has no relevance to the restriction requirement in the instant application because the restriction requirement was not at issue. The binding court opinion *In re Watkinson* is related to the issue of recovering claimed embodiment in a reissue application which was separated from the subject of the issued claims by a restriction requirement. Thus, the restriction requirement remain proper.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-31 and 33-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions of Groups A and B, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claims 32 and 33 are under consideration as they relate to the embodiment of the protein kinase of p38.

The attempt to incorporate subject matter into this application by reference to Accession Number in commercial data base such as NCBI is improper because the data base may change the accession number without referencing the old number, see page 34, paragraph 59 (NCBI data base, AAK1541) and page 35 (data bank access codes 4COX and 2HCK!!!?). Applicants may introduce the referenced sequences into the application by filing a new sequence listing in paper form and a computer readable form (CRF) accompanied by an amendment of the specification to delete the reference to accession numbers from commercial data bases and replace them with a sequence identification number, and a statement by the attorney of record indicating that the sequence listing and the CRF are identical and do not contain new matter. Corrections are required.

The disclosure is objected to because of the following informalities:

- (a) On page 34, paragraph 59, the citation of Wang *et al.* is incorrect. The examiner could not find the article as cited.
- (b) on page 35, line 9, the sentence "The corresponding protein data bank access codes are 4COX and 2HCK, respectively" is confusing and the examiner is not clear to its meaning. The access code is given to unnamed data bank. It appears that the applicants are providing a key to a box in unknown location.

Appropriate correction is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim 33 is objected to under 37 CFR § 1.75(d)(1) as being in improper form because the claim states an improper Markush group. Compounds included within a Markush group must "(1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." (See MPEP § 803.02.) The Markush group is either a polypeptide or a structural element found in protein kinases. Each of the cited protein kinase in claim 33 has a specific utility and structure (amino acid sequence). A compound which occupy one of the inhibitor binding site in protein kinase would not be expected to bind to a similar binding site in a different protein kinase. Thus, the different inhibitor binding sites of the protein kinases listed in the Marekush Group have different structure and function. Applicant must rewrite the claim to remove the improper Markush group.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32 and 33 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

- (a) The phrase "protein kinase inhibitor binding site" in claims 32 and 33 renders the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The phrase has at least two meaning to this examiner. The first is a polypeptide comprising the protein kinase binding domain by itself, e.g., residues 78-336 of, presumably, SEQ ID NO: 1. The second meaning is the structure of the

protein kinase inhibitor binding site which is a non-statutory subject matter (see below).

- (b) Claim 32 contains references to amino acid residues in an amino acid sequence which corresponds to the amino acid sequence of p38, but the amino acid sequence of p38 is not identified by a sequence identification number which renders the claim indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The phrase has at least two meaning to this examiner.
- (c) Claim 32 attempts to define the protein kinase inhibitor binding site by identifying three dimensional structure elements, but the specification contains no atomic coordinates for any protein kinase including p38 (the reference structure) which renders the claim indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The structure p38 is poorly described in the specification and the structure element L7 and  $\beta$ L16 are not even identified in Figures 3A or 3B.
- (d) Claims 33 contains references to several specific proteins which are not identified by sequence identification numbers which renders the claim indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.

35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 32 and 32 are rejected under 35 U.S.C. § 101 because the claimed invention is directed toward non-statutory subject matter.

If the claim is directed to a protein kinase/polypeptide comprising an inhibitor binding site, the following rejection apply under 35 U.S.C. § 101. In the absence of the hand of man, naturally occurring proteins and/or nucleic acids are considered non-statutory subject matter. *Diamond v. Chakrabarty*, 206 USPQ 193 (1980). The claims reads on any natural and allelic variants of a protein kinase comprising an inhibitor binding site as defined in claim 32. This rejection may be overcome by amending the claims to contain wording such as "An isolated and purified protein or nucleic acid".

If the claim is directed to an inhibitor binding site, the following rejection apply under 35 U.S.C. § 101. An inhibitor binding site is an intrinsic property of a protein kinase. Claim directed to a protein having specific property such as amino acid sequence, catalytic properties, molecular weight, and three dimensional structure and/or structural elements

thereof are statutory subject matter because the claim is directed to a composition of matter. On the other hand, claims directed to a property of a protein such as a three dimension structure or part thereof are not patentable subject matter because they are not a process, machine, manufacture, or composition of matter.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 32 is directed to all possible "protein kinase inhibitors binding sites". The specification, however, only provides a single representative species of the inhibitor binding site from rat p38. The specification fails to disclose the three dimensional structure of any protein kinase, let alone the inhibitor binding site. Although the specification contains nice pictures showing the inhibitor bound to its binding site of the rat p38 and the three dimension structure of p38 (Figures 3-6), the specification contains no atomic coordinates of any protein kinase including those of p38, and therefore one of ordinary skill in the art would not be able to construct the inhibitor binding site. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these protein kinase inhibitor binding sites by any identifying structural characteristics or properties other the structural element in claim 32, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claim 32 is rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is **not even** enabling for the inhibitor binding site of p38. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to the inhibitor binding site of any protein kinase, presumably, said inhibitor binding site is not one of the substrates binding site. Factors to be considered in determining whether

undue experimentation is required, are summarized *In re Wands* [858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses either a polypeptide comprising an inhibitor binding site or the inhibitor binding site as defined by its structural element. The specification provides guidance and examples in the form of an assay to crystallize the p38 protein and soak the resulting crystal in a solution comprising one of the two compound shown in Figure 2 (see examples). While molecular biological techniques and genetic manipulation to make and use the constructs claimed are known in the prior art and the skill of the artisan are well developed, knowledge regarding all the protein kinases from any biological source which may have an inhibitor binding site, and their three dimensional structure is lacking. Thus, searching for a protein kinase having a inhibitor binding site with structural element described in claim 32 is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation to identify a protein kinase inhibitor binding site have the specific structural element listed in the claim is enormous. Since routine experimentation in the art does not include screening vast numbers of biological source for a desired protein kinase or crystallization conditions where the expectation of obtaining the desired protein kinase inhibitor binding site is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the biological source of the protein kinase/inhibitor binding site, and crystallization conditions to obtain an adequate crystal suitable for structure determination. Without such a guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 32 and 33 are rejected under 35 U.S.C. § 102(b) as being anticipated by Wilson *et al.* [J. Biol. Chem. 271, 27696-27700 (1996)].

Wilson *et al.* teach human p38 $\alpha$  having the amino acid sequence shown in Figure 1. If the claims are directed to a p38 polypeptide comprising an inhibitor binding site other than that of the substrates binding sites, the claimed binding site is an intrinsic property of the human p38 (claims 32 and 33). Also, Wilson *et al.* teach the three dimensional structure of the human p38 $\alpha$ , see Figure 2. In particular, it teaches the atomic coordinates of the structure which has been deposited in the protein data bank at Brookhaven National Laboratory (code number 1WFC), see the foot not on page 27696, left column. Although the Wilson *et al.* do not teach specifically the p38 inhibitor binding site defined by claim 32, said inhibitor binding side is an intrinsic property of the p38 and its model shown in Figure 2.

Claims 32 and 33 are rejected under 35 U.S.C. § 102(e) as being anticipated by U. S. Patent 6,387,641 [(641), Bellon *et al.*].

The 641 patent teaches human phosphorylated p38 $\gamma$  of SEQ ID NO: 1, see the abstract and SEQ ID NO: 1. If the claims are directed to a p38 polypeptide comprising an inhibitor binding site other than that of the substrates binding sites, said binding site is an intrinsic property of the human p38. Also, the 641 patent teaches the three dimensional structure of the human phosphorylated p38. In particular, it teaches the atomic coordinates of the structure in Figure 1-1 to 1-137, and the structure is shown in Figures 2 and 3 (different views). Although the 641 does not teach specifically the p38 inhibitor binding site as defined by claim 32, Figure 2 shows the inhibitor binding site claimed in this application which is an intrinsic property of the structure, the upper left corner of the structure and marked the hinge region.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is (703) 305-6586. The examiner can normally be reached Monday, Tuesday, Thursday, and Friday from 9:00 a.m. to 5:30 p.m.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone numbers for this Group are (703) 305-3014 and (703)308-4242.



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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

  
Nashaat T. Nashed, Ph. D.  
Primary Examiner